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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,789	10/11/2005	Henri Tiedge	1181-13 PCT US	2634

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EXAMINER	
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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,789	TIEDGE, HENRI	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-20* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 8-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/16/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 3/14/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's amendment to the claims filed 7/16/08 is acknowledged. The amendment adds new claim 20. With entry of the amendment, claims 1-6 and 8-20 are pending in the application.

Claims 5, 6, and 8-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-4 and 17-20 are under consideration.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112, first paragraph (enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

As amended on 7/16/08, the claims are drawn to pharmaceutical compositions for administration to an animal subject comprising a therapeutically effective amount of an antisense oligonucleotide targeted to a sequence in SEQ ID NO:1, which corresponds to the 200-nucleotide sequence of the non-translatable RNA BC200. In certain embodiments the target sequence in SEQ ID NO:1 is the sequence defined by SEQ ID NO:2, corresponding to residues

156-200 of BC200. In other embodiments, the antisense oligonucleotide is SEQ ID NO:3 or 4, which target residues 156-185 and 158-178, respectively, of BC200 RNA. In Claim 20 the animal subject is a human.

MPEP 2164.01(c) states when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

In the instant case the "pharmaceutical composition," "administration to an animal subject," and "therapeutically effective amount" language in combination with the disclosure in the specification (pages 36-39), stating the antisense oligonucleotide compositions may used to treat neurological diseases, including Alzheimer's, Parkinson's, Downs' syndrome, and epilepsy, requires these claims be evaluated to determine whether the specification teaches how to use these compositions in the manner intended.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. See MPEP 2164.01.

In reviewing the instant application, parent applications, and prior art, the Examiner finds 1) no evidence of a nexus between the reduction of BC200 levels, as by antisense-mediated degradation of BC200 RNA, and the remediation of any neurological condition or cancer; 2) that residues 1-122 of BC200 RNA are highly homologous to Alu repetitive elements which are found in high copy numbers in primate genomes (page 5 of 60/425475), and that therefore antisense oligonucleotides against residues 1-122 of BC200 RNA, as embraced by instant claim

1, would likely hybridize to a number of off-target elements as well as BC200 RNA; and 3) that at the time of filing the delivery of therapeutically effective amounts of antisense oligonucleotides to cells in vivo in a living animal, especially cells in the central nervous system, was highly unpredictable.

With regard to point 1, at the time of filing neither the instant specification nor the prior art provide any evidence or representative examples showing or reasonably suggesting that the inhibition of BC200 activity can be used to treat any neurological disease or cancer. While the specification shows that BC1 expression is reduced following epileptiform activity (page 65), there is no disclosure showing or teaching how or why this fact enables one of skill to use BC200 antisense to treat any of the different neurological diseases suggested. There are no working examples in the specification remotely correlative of the intended use in any animal subject, much less a human. While the prior art suggested that BC200 RNA may be associated with brain function, and while the Tiedge patents 5,670318 and 5,736,329 taught a diagnostic correlation between BC200 RNA and cancer and Alzheimer's, there is no disclosure showing that the addition of nucleic acids antisense to the non-translated BC200 sequence may be used to treat any disease in any animal subject. For example, there is no evidence showing or reasonably suggesting that normal expression or abnormal overexpression of BC200 RNA triggers, promotes, or exacerbates any neurological disease. Similarly, there is no evidence showing that reducing BC200 RNA levels alleviates disease or has any positive effect on an animal suffering from any neurological disease. While the prior art teaches BC200 is an interesting target for further research, there is no disclosure showing that reducing BC200 levels alleviates the symptoms of a disease. The fact that BC200 RNA is diagnostic of a disease provides no direct

correlation to the role BC200 plays a role in the disease itself. While the BC200 expression level may serve as one index of the disease, the idea that directly interfering with BC200 activity will alleviate the disease would appear to be speculative at the time of effective filing, 11/12/2002, and the examiner finds no post-filing evidence to substantiate the assertions in the specification that antisense-mediated knockdown of BC200 has any type of treatment effect in any animal. Accordingly, it is reasonable to question the objective truth of the assertions made in the specification stating the claimed antisense may be used to treat Alzheimer's or any other neurological condition, or cancer. A nexus between the intended use and effects is not found. Without such direction or guidance, the specification provides little more than a starting point for further research, wherein one of skill would be left to de novo trial and error experimentation with no assurance the claimed antisense could in fact be used in a manner correlative with the scope now claimed.

With regard to point 2, prior filed Provisional Application 60/425475 teaches that the primary sequence of BC200 RNA can be subdivided into three structural domains, I, II, and III, and that Domain I, nucleotides 1-122, is substantially homologous to Alu repetitive elements found in high copy numbers throughout the primate genome (page 5). Accordingly, it is unclear how one of skill may achieve a sequence-specific, predetermined biological effect in a cell in an animal by infusing or administering an antisense complementary to this region without generating a host of off-target effects in addition to those having to do with the inhibition of BC200. Again, there are no examples showing how antisense targeted to this region of BC200 may be used to treat disease. The likelihood of off-target effects generated by such antisense also

casts doubt on the objective truth of the assertion these antisense may be used pharmaceutically to produce a specific desired effect of treating a neurological disease or cancer.

Finally, with regard to point 3, problems related to the pharmaceutical use of antisense nucleic acids were well known in the art at the time of invention. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Opalinska et al. (2002) *Nature Reviews* 1 :503-514 teach that

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511)

This problem is particularly pertinent to the instant claims since a primary use involves the treatment of neurological disease. Thus, the antisense molecules must be delivered into target cell in the CNS. There is no disclosure in the specification showing how to deliver therapeutically effective amounts of the claimed antisense across the blood brain barrier into cells in the brain to achieve the intended effects.

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the compositions to treat any organism, mammal, or human subject. Instead, the specification makes general assertions that one of skill in the art would know how to apply (dose, frequency, and duration) the antisense oligos to the lungs. Examples of in vivo use of the pharmaceutical compositions, working or otherwise, are not provided.

Given these teachings, and lack thereof, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" and "administration to an animal" language from the instant claims would overcome this rejection.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 and 17-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,670,318 in view of

Ellington et al. (1998) "Synthesis and Purification of Oligonucleotides" in *Current Protocols in Molecular Biology* 2.11.1-2.11.25 (John Wiley & Sons, Inc.);

Beaucage (1993) "Oligodeoxyribonucleotides synthesis. Phosphoramidite approach" *Methods in Mol. Biology* 20:33-61; and

Caruthers et al. (1987) "Chemical synthesis of deoxyoligonucleotides" *Methods in Enzymology* 154:287-313.

Claim interpretation:

MPEP 2111.02 states that if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

In the instant case the limitations "pharmaceutical composition for administration to an animal subject" and "antisense molecule" are considered to represent intended uses. The body of the claims fully sets forth the complete structure of the nucleic acid molecule and the composition containing said molecule. The claims are drawn to a composition of matter, not a method of using said composition. As a result, any disclosure in the prior art teaching or suggesting the preparation of the claimed nucleic acid molecule in a pharmaceutically acceptable carrier is sufficient to anticipate and/or render obvious the instantly claimed composition. Such a composition is necessarily a pharmaceutical composition, whether it is used pharmaceutically or not. It is not necessary for the prior art to teach the composition for the same purpose. If the composition is disclosed, every property inherent to that composition is also disclosed, even if all such properties were not recognized by the prior art.

It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

The mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound, but no utility need be disclosed by the reference. *In re Schoenwald,* 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992). See MPEP 2122.

The rejection:

U.S. Patent 5,670,318 claims oligonucleotide probes that are identical to instantly claimed antisense sequences SEQ ID NO:3 and 4. US Patent 5,670,318 further claims oligonucleotide probes that hybridize to residues 156-185 of a BC200 RNA target sequence, referred to therein as SEQ ID NO:1, that is identical to instantly recited SEQ ID NO: 1.

Accordingly, US Patent 5,670,318 necessarily also claims probes that hybridize to instantly recited SEQ ID NO:2. Thus, the probes claimed in US Patent 5,670,318 are structurally identical to the sequences claimed in the instant application.

With regard to instant claims 17-19, drawn to isolated antisense oligonucleotides in pharmaceutically acceptable carriers and to kits thereof, it was well known in the prior art to package probes and other diagnostic reagents, routinely used in the laboratory, in the form of kits to save time and expense. Further, the term "Kit" is not limited by either the claims or the specification to commercially purchased materials but is broadly interpreted to include any compartmentalized arrangement of the probes in enclosed vessels and/or carriers prepared by the artisan according to routine practice.

US Patent 5,670,318 does not teach “pharmaceutical compositions" comprising said probes.

The instant application defines "pharmaceutically acceptable carriers" at page 35 as "any and all solvents, buffers, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are non-toxic to a subject."

Methods for preparing oligodeoxynucleotide probes and primers were well known in the art, as shown by Ellington et al., Beaucage, and Caruthers et al. These methods taught preparing probes and primers in pharmaceutically acceptable diluents.

Ellington et al. taught chemical synthetic methods for making and purifying oligonucleotides of virtually any desired sequence. At page 2.11.14 it is taught that following synthesis and deprotection, the oligonucleotides can precipitated and washed with 95% ethanol, dryed, and then resuspended in water. Absent objective evidence to the contrary, water is considered to be a “pharmaceutically acceptable” carrier.

Alternatively and in addition Ellington et al., Beaucage et al. taught methods for making and purifying oligodeoxynucleotides, wherein the oligonucleotide is finally purified by PAGE, followed by G25 size exclusion chromotagraphy, wherein the oligonucleotide is eluted and pooled with doubly distilled water (page 45). Beaucage et al. taught that oligonucleotides purified in this manner are suitable for in vitro biochemical experiments (page 46). Beaucage et al. also describe HPLC and ion-exchange methods of purification, which also involve elution with and final storage in distilled water.

Caruthers et al. taught that following preparation synthetically oligonucleotides can be purified with reverse phase HPLC, washed, dryed, and resuspended in 10 mM Tris-HCl (pH 7.6), 1mM EDTA, and that oligonucleotides purified according to this method can be used directly in biochemical experiments (pp. 309-310).

Accordingly, methods for making and using DNA probes were well known in the prior art. As shown by the prior art, it was normal laboratory practice to purify and collect the final oligonucleotide product in doubly distilled water or Tris-EDTA buffers. Absent evidence to the contrary, water and Tris-EDTA are pharmaceutically acceptable diluents. Thus, by definition, the probes claimed in US Patent 5,670,318 would necessarily be prepared as "pharmaceutical compositions" according to the broadest reasonable interpretation of the scope and meaning of the term "pharmaceutical composition," which is considered to include carriers such as water and Tris-HCL, EDTA.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting patent.

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The recent U.S. Court of Appeals Federal Circuit decision in *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 86 USPQ2d 1001 (Fed. Cir. 2008) makes it clear that the protection afforded by 35 USC 121 applies only to divisional applications filed as the result of a restriction requirement. Accordingly, methods of using the instant antisense sequences also render obvious the sequences themselves.

Claims 1-4 and 17-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,736,329 in view of

Ellington et al. (1998) "Synthesis and Purification of Oligonucleotides" in *Current Protocols in Molecular Biology* 2.11.1-2.11.25 (John Wiley & Sons, Inc.);

Beaucage (1993) "Oligodeoxyribonucleotides synthesis. Phosphoramidite approach" *Methods in Mol. Biology* 20:33-61; and

Caruthers et al. (1987) "Chemical synthesis of deoxyoligonucleotides" *Methods in Enzymology* 154:287-313.

U.S. Patent No. 5,736,329 claims methods for testing for the presence of Alzheimer's disease using oligodeoxynucleotide probes that hybridize to BC200 RNA. The probes used in the method are identical to those sequence now claimed in the instant application.

Accordingly, the sequences themselves are prima facie obvious, since they are essential to the practice of the claimed method. Kits containing these probes are similarly prima facie obvious, since it was normal practice in the art to prepare and store reagents beforehand for convenience and ease of use in later experiments.

U.S. Patent No. 5,736,329 does not claim pharmaceutical compositions.

However, for all the reasons given above in the ODP rejection over U.S. Patent No. 5,670,318, chemical synthetic methods for preparing oligonucleotide probes were well known in the art. As shown by Ellington et al., Beaucage, and Caruthers et al., which are relied on for the reasons given above, chemically synthesized probes were typically collected and/or resuspended in pharmaceutically acceptable diluents such as distilled water or low concentration Tris-HCl (pH 7.6), EDTA buffers. These compositions were also said to be suitable for, at least, biochemical experiments in vitro.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting patent.

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Claims 1-4 and 17-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19 of copending US Patent Application 10/503782 in view of

Tiedge (US Patent 5,670,318);

Ellington et al. (1998) "Synthesis and Purification of Oligonucleotides" in *Current Protocols in Molecular Biology* 2.11.1-2.11.25 (John Wiley & Sons, Inc.);

Beaucage (1993) "Oligodeoxyribonucleotides synthesis. Phosphoramidite approach" *Methods in Mol. Biology* 20:33-61; and

Caruthers et al. (1987) "Chemical synthesis of deoxyoligonucleotides" *Methods in Enzymology* 154:287-313.

Copending Application 10/503782 claims methods for testing whether a breast carcinoma has an invasive phenotype comprising combining the test sample with an oligonucleotide probe capable of hybridizing with human BC200 RNA.

Tiedge et al. taught probes capable of hybridizing to BC200 RNA identical to those sequences now claimed for detection and diagnostic purposes.

Tiedge et al. further taught kits comprising these probes (col. 5).

Copending Application 10/503782 does not claim pharmaceutical compositions.

However, as shown by Ellington et al., Beaucage, and Caruthers et al., which are relied on for the reasons given above, chemical synthetic methods for preparing oligonucleotide probes were well known in the art. As shown by Ellington et al., Beaucage, and Caruthers et al., chemically synthesized probes were typically collected and/or resuspended in pharmaceutically acceptable diluents such as distilled water or low concentration Tris-HCl (pH 7.6), EDTA buffers. These compositions were also said to be suitable for, at least, biochemical experiments in vitro.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiedge et al. (US Patent 5,670,318) in view of

Ellington et al. (1998) "Synthesis and Purification of Oligonucleotides" in *Current Protocols in Molecular Biology* 2.11.1-2.11.25 (John Wiley & Sons, Inc.);

Beaucage (1993) "Oligodeoxyribonucleotides synthesis. Phosphoramidite approach" *Methods in Mol. Biology* 20:33-61; and

Caruthers et al. (1987) "Chemical synthesis of deoxyoligonucleotides" *Methods in Enzymology* 154:287-313.

The claims are interpreted as explained above in the ODP rejection over US Patent 5,670,318.

Tiedge et al. disclosed oligonucleotide probes that hybridize to a BC200 RNA target sequence identical to instant SEQ ID NO:1 for diagnostic purposes (cols. 1-5). The probes are identical to instantly claimed antisense sequences SEQ ID NO:3 and 4 (see the sequences set

forth at the top of column 3). Additionally, Tiedge et al. specifically taught probes complementary to instant SEQ ID NO:2 (see column 2, bottom).

While Tiedge et al. do not specifically teach using these probes for inhibition of BC200 RNA expression, the sequences are identical to the "antisense" sequences now claimed. Therefore, all properties inherent to these sequences, whether recognized or not, were disclosed and in the public domain more than one year before the filing date of the instant application. Because the disclosed sequences are identical to those now claimed in claims 3 and 4, the disclosed sequences necessarily possess antisense properties and *de facto* are antisense to the target recited in instant claims 1 and 2. For example, instant SEQ ID NO:4 is identical to SEQ ID NO:7 in Tiedge et al., which specifically hybridizes with instant SEQ ID NO:1 and 2, also identical to SEQ ID NOs. 1 and 2, respectively in Tiedge et al.

[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Applicant is not claiming a method of use, but the product itself. The term "antisense", used in the instant claims, is merely an intended use that does not clearly impose any structural limitations distinguishable from those sequences set forth by Tiedge et al. Clearly, the claimed antisense molecules include those disclosed by Tiedge et al. as evidenced by a comparison of the sequences claimed in instant claims 3 and 4 with those disclosed by Tiedge et al. for use as diagnostic probes.

While Tiedge et al. do not teach "pharmaceutical compositions" *per se*, Tiedge et al. taught that the oligonucleotide probes of their invention could be synthesized using conventional chemical synthetic methods known in the art (col. 4, lines 5-10). As shown by Ellington et al., Beaucage, and Caruthers et al., it was normal laboratory practice to elute, resuspend, and store chemically synthesized oligonucleotide probes in "pharmaceutically acceptable" diluents such as distilled water or Tris buffer.

Accordingly, the instantly claimed pharmaceutical compositions are prima facie obvious as the preparation of the BC200 oligonucleotide probes disclosed by Tiedge et al. would necessarily involve washing, eluting, and/or resuspending said probes in an aqueous solvent, water or buffer of physiological pH for subsequent analysis and use as a biochemical reagent.

Thus, in view of the definition given at page 35 of the instant specification, embracing any non-toxic buffer or solvent, and in view of the protocols disclosed in the prior art establishing that it was routine and customary for practitioners to prepare DNA probes in non-toxic buffers such as water and Tris-EDTA, it would have been obvious to one of skill in the art at the time that the types of buffers and solvents implicitly and inherently disclosed and suggested by Tiedge et al. for making and storing the anti-BC200 DNA probes would necessarily

be pharmaceutically acceptable inasmuch as they would be compatible with at least one use in vivo.

Accordingly, the mere formulation of the claimed antisense oligonucleotides in a pharmaceutically acceptable carrier *per se* does not patentably distinguish the claimed products over those disclosed by Tiedge et al. Moreover, specific motivation to formulate in a pharmaceutically acceptable carrier is not particularly relevant since it would have been clear to the ordinary practitioner the probes disclosed by Tiedge et al. must be dissolved in some buffer or solvent and that many buffers and solvents, and since there is evidence to suggest (Ellington, Beaucage, and Caruthers.) that at least one acceptable buffer known in the prior art for use with probes included a solvent likely to be pharmaceutically acceptable.

Thus, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to arguments

Applicant argues the prior art does not suggest formulating the molecules of Tiedge for use in an animal subject.

The argument is not persuasive because the instant claims are drawn to compositions of matter not methods of use. As explained above the prior art reasonably teaches the compositions as now claimed for diagnostic purposes. Prior art teaching or suggesting the claimed composition with all its limitations for any purpose is sufficient to anticipate or render obvious the composition since the prior art need not teach the composition for the same purpose. Simple formulation of the probes disclosed by Tiedge in a buffer suitable for pharmaceutical use fails to

distinguish the claimed composition from those that would have normally been prepared during the course of routine synthesis and purification of the probes disclosed by Tiedge. The fact that Applicant may have discovered the probes may also be used to inhibit BC200 activity does not by itself render the compositions patentable since these properties are inherent to the molecules previously disclosed by Tiedge in the 5,670,318 Patent. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, AU1635
October 3, 2008